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(12) # EUROPEAN PATENT APPLICATION

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(54) Vascular prostheses, conditioning method for dry conservation and surgical application

(57) This supple vascular prosthesis of synthetic or biological origin can be conserved in the dry state. It contains at least 10 wt-% water (with respect to the weight of the dry prosthesis) and at least 10 wt-% of a biocompatible compound, which is not very volatile and is capable of retaining water.

To condition the prostheses of synthetic or biological origin for dry conservation, the prosthesis is soaked, at ambient temperature, in an aqueous bath in which there is a biocompatible, compound having low volatility, so that it retains water such that, after drying, it contains at least 10 wt-% water and 10 wt-% of the aforesaid compound with respect to the weight of the dry prosthesis.

These prostheses are utilized in vascular cardiovascular surgery.

Vascular prostheses, conditioning method for dry conservation and surgical application

This invention concerns vascular prostheses based on collagen of different biological origins, which may be venous homografts, bovine heterografts, treated umbilical veins or synthetic vascular prostheses with a cloth sheathing on which a protein layer is fixed.

The prostheses used to date are conserved in glass tubes, immersed in a bactericide solution or an alcohol-based solution which affect their biocompatiblity.

In vitro tests, in particular the method involving organotypical culture of chicken embryo aortas, gave deceptive results. In general, one may say that, in spite of repeated rinsing of the prostheses before they are used, conservation media based on ethanol or glutaraldehyde or other bactericides have been shown to be cytotoxic *in vivo*.

Furthermore, while the conservation of such prostheses in physiological serum provides them with suitable biocompatibility concerning cellular growth, it is probable that the cicatrization cannot be accompanied by neoendothelialization after implantation; in effect, the cellular covering adheres only poorly to the support in this case.

Since 1968 prostheses of polyester fiber have been used in the form of a woven or knotted honeycomb fabric, having a smoothed [velvety] interior or exterior and prepared in the form of tubes or sheets. Before such prostheses are used, they must be pre-coagulated with the blood of the patient. Blood fibrin makes the walls of the prosthesis impermeable to blood (impedes the escape of blood to neighboring tissues) and creates a smooth surface in the interior of the blood vessel, but this necessitates neutralization of the thrombin formed during the pre-coagulation. Such prostheses are stored in the dry state, in sterile packages, but their preparation before use is long and delicate.

An improvement in synthetic prostheses resulted from their being made impermeable by means of a layer of various proteins such as collagen, albumin, fibronectin, gelatin, elastin and others; however, the proteins must be solidly anchored to the fabric and it is necessary to immerse the fabric prosthesis in a solution of the selected protein and to thereby fix it to the fabric through chemical bonding, *e.g.*, through the use of glutaraldehyde or diphenylcarbodiimide. This process is know to those familiar with the art.

It is known that prostheses which are thus rendered impermeable are stiff and brittle and that they cannot be conserved in the dry state; if they are conserved in a liquid environment, they display the same disadvantage as grafts of biological origin, they are cytotoxic.

The present invention allows this disadvantage to be remedied; in effect, it allows prostheses of biological or synthetic origin to be conserved in the dry state, in a supple form, due to a conditioning treatment.

The French Patent 71 16 082 describes a "process for treating a collagen fiber, the resulting fiber and its application", which consists of bringing the fiber in contact with at least one distilled water bath and an agent capable of maintaining the humidity of the fiber by impeding evaporation of the water which it contains.

Surprisingly, it has been found that a treatment of the same kind, but adapted to the preparation of prostheses, is applicable to the production of vascular prostheses, thus avoiding the inherent disadvantages of the prior method and doing away with the need to condition the prostheses in the presence of a liquid.

The first object of this invention is thus a prosthesis of biological or synthetic origin to which a protein is fixed, which is supple in spite of it being conserved in a dry state and which contains at least 10 wt-% of water and 10 wt-% with respect to the weight of the dry prosthesis of a biocompatible compound of low volatility, and which retains water. These prostheses can be conserved after sterilization, to protect against contamination, without being held in a liquid medium, which is an advantage of this invention.

The other advantage of this invention is the fact that the specialist does not need to subject the prosthesis to any pretreatment before implanting it *in vivo*; because of its suppleness and the absence of cytotoxicity, he may use it as commercialized.

This result was entirely unexpected.

Another object of this invention is the process of rendering supple and conditioning vascular prostheses of biological or synthetic origin by immersion in an aqueous solution containing a biocompatible compound of low volatility, and which retains water; this conditioning process may be followed by a conventional sterilization by any method known to the art.

This invention thus concerns a prosthesis permanently containing an amount of water equal to at least 10 wt-% with respect to the weight of the dry prosthesis, and at least one low volatility compound having a strong affinity for water and particularly capable of retaining water in the prosthesis in the absence of any liquid environment, the said compound being present at a concentration of at least 10 wt-% and preferably at least 15 wt-% with respect to the weight of the dry prosthesis and having a molecular weight not exceeding about 400.

The aforesaid compounds, acting as conditioning agents capable of retaining water in the vascular prosthesis, may be present in a surface layer and/or the bulk of the prosthesis. They have a strong affinity for water and are more or less hygroscopic.

Their presence as well as the presence of water in or on the prosthesis provides the latter with a certain suppleness which is maintained in storage.

In some instances, the properties of the prosthesis may be improved by incorporating a biocompatible antiaggregant, anticoagulant, antiseptic, bactericidal or similar compound or mixtures thereof in the conditioning bath of this invention; these products will be absorbed by the prosthesis along with the water and the conditioning agent.

The conditioning agents of organic origin must be well tolerated by human tissues and hence be biocompatible and hemocompatible.

Such conditioning agents may be selected from among the fatty alcohols and acids, their esters and ethers, alcohols and polyalcohols having a low volatility at ambient temperature, and their polycondensation derivatives such as polyoxyalkylene glycols having a molecular weight of less than about 400 and their mixtures. Among the preferred compounds one may list glycerol, glycols, polyoxyethylene glycol.

The amount of the conditioning agent evidently varies with the nature of the latter and the kind of prostheses being treated. The amount of agent in the prosthesis is in general about equal to the amount of water. One familiar with the art may readily determine the optimum relative proportions of water and a particular conditioning agent based on preliminary tests.

It should be noted that the combination of water with a conditioning agent is indispensable to obtaining the results of this invention. In fact, even a hygroscopic conditioning agent such as glycerol is incapable of being absorbed by the prostheses in the absence of water.

Furthermore, water when used by itself is absorbed by the prosthesis but cannot remain there in a lasting manner, for it evaporates soon after its application after the prosthesis leaves the liquid environment. According to this invention, the combination of water and conditioning agent allows for penetration of the agent into the prosthesis as well as retention, during storage, of the water which simultaneously penetrates the prosthesis.

The molecular weight of the conditioning agent mixed with water has a direct influence on the swelling of the prosthesis; the higher the molecular weight of the prosthesis the lower is the amount of liquid absorbed; on the other hand, the swelling is not any more permanent if the molecular weight of the agent is higher than 400.

To obtain a supple prostheses of this invention, capable of being preserved without a liquid environment, one may for instance operate by immersing the prosthesis in a bath comprising a mixture of water and the conditioning agent. The conditioning agents may be applied in solution, in an emulsion or in aqueous suspension or in a third solvent.

The temperature at which the prosthesis is impregnated by the conditioning bath may be between 10 and 50°C and one may deviate from this temperature range without any disadvantage as long as the bath remains liquid.

The treatment time may vary from one second to several days, depending on the nature of the conditioning agent and its concentration in the solution. In general, durations of 10 minutes to 8 hours are suitable. The treatment time evidently depends on factors such as the temperature, the nature of the prosthesis and the desired degree of suppleness.

It is not outside the scope of this invention if the soaking of the prostheses in the conditioning bath occurs at a pressure which is either higher or lower than atmospheric pressure; one thus facilitates "debubbling" or degassing.

It is preferable to maintain the pH of the conditioning bath within certain limits, so that, after sterilization, the pH of the prosthesis is near neutral; a pH between 5 and 9 is suitable.

If the conditioned prostheses are sterilized with ethylene oxide, the pH increases slightly during the sterilization. It is preferable to compensate for this variation by introducing a weak acid such as acetic acid, which will be absorbed in the prosthesis, into the conditioning bath.

The sterilization may also be performed by irradiation and, in this case, no pH correction is needed.

Aside from the material for modifying the pH, the conditioning bath may contain antiaggregants, anticoagulants, antiseptic bactericides or similar substances. The prostheses will absorb these substances during the process of this invention, which renders them supple, thus imparting new properties, which is another advantage of this invention.

One of the advantages of this invention results from the fact that the sterilization of the prostheses which occurs after their conditioning is facilitated by the presence of water in the prostheses; it is for instance known that the sterilization with ethylene oxide is not expedient unless the article to be sterilized contains a certain humidity.

After their the treatment to render them supple and their sterilization, the prostheses may be preserved as if they were dry, *i.e.*, without being in a liquid, and they need only to be packaged in a material which does not allow microorganisms to pass. It is thus possible to use packaging materials of plastic, treated paper or cardboard in the form of a rigid or thermoformed case.

In addition, the prosthesis may be sterilized in its package by means of a gas or radiation known to be capable of sterilizing.

The conditioning of the prostheses of this invention is convenient for the manufacturer as well as the user.

The sterile conservation of the prostheses treated according to this process is not affected by their conditioning process and the process which renders them supple, but it depends only on the nature of the prosthesis.

Any manipulations to remove alcohol or other prosthesis preserving liquids prior to utilization are made unnecessary. The prostheses are supple and are easy to use.

The prostheses of this invention are not cytotoxic; in the contrary, *in vivo*, after implantation, they favor the growth of cells of different types and origin on their surface. *In vivo* implantations of treated materials of this invention induce good cellular affinity and improve cellular colonization of the prostheses.

This invention will now be illustrated, without being limited in any way, by the following examples:

Example 1

A conditioning bath having the following composition is used:

Glycerin	60 parts by weight
Distilled water	40 parts by weight
Citric acid	0.05 parts by weight

A homograft is selected, prepared and rendered antigenic by a known process. It is then gaged, placed on a protector so that it does not lose its shape and then immersed at room temperature in the conditioning bath described above.

After immersion for 8 hours, it is drained, and after drying for several hours it is packed in working condition for thermoforming, then sterilized either with ethylene oxide or ionizing radiation.

The user may utilize this homograft as it comes out of its package, *e.g.*, for a vascular bypass.

Similar results are obtained by treating a bovine heterograft or an umbilical vein in the same manner as described above. These prostheses may be utilized for a vascular bypass.

Example 2

A tubular prosthesis of honeycomb, knit polyester is soaked in a buffer solution at pH 7.4, containing 9% albumin and 1.5% glutaraldehyde.

After immersion for 15 minutes, the prosthesis is allowed to drain and dry, and it is then immersed for 3 hours at ambient temperature in a conditioning bath like that described in Example 1.

The prosthesis becomes supple and remains supple during storage.

Example 3

A tubular prosthesis of honeycomb, small chain knit polyester, is soaked in a buffer solution at pH 7.4, containing 10% of a mixture of equal weights of collagen and albumin. After reticulation and drying, the prosthesis is rendered supple by soaking for 2 h 30 min in a conditioning bath like that described in Example 1.

After conditioning and sterilization, the prosthesis may be utilized immediately or stored. It is supple, readily usable, does not require precoagulation, is not cytotoxic and favors neoendothelialization.

Example 4

Conditioning bath:

Diethylene glycol	65 parts by weight
Distilled water	35 parts by weight

Example 5

Conditioning bath:

Trishydroxymethylpropane	50 parts by weight
Distilled water	50 parts by weight

Example 6

Conditioning bath:

Glycerol	50 parts by weight
Distilled water	50 parts by weight
Heparin	10,000 units

The prostheses which are thus conditioned have temporary localized anticoagulant properties.

Example 7

Conditioning bath:

Glycerol	60 parts by weight
Distilled water	50 parts by weight
Acetylsalicylic acid	0.5 parts by weight

The prostheses which are thus conditioned have temporary localized anti-plaque forming properties.

CLAIMS

1. Supple vascular prostheses of biological or synthetic origin, capable of being conserved in the dry state, characterized in that they contain at least 10 wt-% of water and at least 10 wt-% of a biocompatible compound of low volatility with respect to the dry weight of the prosthesis.

2. Prostheses according to Claim 1, characterized in that the water retaining compound has a molecular weight of less than about 400 and is selected from among the fatty alcohols and acids, their esters and ethers, alcohols and polyalcohols having low volatility at room temperature and their polycondensation derivatives, such as polyoxyalkylenes, glycols and their mixtures.

3. Prostheses according to Claim 2, characterized in that they contain 10 to 50 wt-% of water with respect to the weight of the dry prosthesis.

4. Prostheses according to any one of the foregoing Claims, characterized in that the water retaining compound is a polyol selected from among glycerol, diethylene glycol and tris-hydroxymethyl propane.

5. Prostheses according to any one of the foregoing Claims, characterized in that the water retaining compound represents 10 to 70 wt-% of the weigh of the dry prosthesis.

6. Prostheses according to any one of the foregoing Claims, characterized in that the water and the water retaining compound are localized in the bulk of the prosthesis.

7. Synthetic prostheses with sheathing of a synthetic textile, on which a layer of protein has been fixed by chemical bonding, characterized in that the water and the water retaining compound are localized in the aforesaid layer.

8. Prostheses according to any one of the foregoing Claims, characterized in that they contain, among others, antiaggregant, anticoagulant, antiseptic, bactericidal or antibiotic biocompatible compounds or their mixtures.

9. Conditioning process for prostheses of synthetic or biological origin, for the purpose of conservation in the dry state, characterized in that the prosthesis is subjected to soaking, at ambient temperature, in an aqueous bath, wherein there is a biocompatible compound of low volatility, which retains water so that, after drying, it contains at least 10 wt-% of water and 10 wt-% of the aforesaid compound with respect to the weight of the dry prosthesis.

10. Process according to Claim 9, characterized in that, after conditioning and drying, the prosthesis is sterilized by exposure to a gas or radiation.

11. Process according to one of the Claims 9 or 10, characterized in that antiaggregant, anticoagulant, antiseptic, bactericidal or antibiotic substances or their mixtures are added to the conditioning bath.

12. Application of the prostheses according to one of the foregoing claims 1 to 8, in vascular or cardiovascular surgery.

Translation: J. Beutel
April 16, 1998

EUROPEAN RESEARCH REPORT

DOCUMENTS CONSIDERED TO BE PERTINENT			
Category	Citation of the document and, if necessary, indication of the pertinent parts	Claim No.	Classification of the Application (Int. Cl.[4])
X	US-A-4 357 274 (H. W. Heinz) * Co. 2, lines 30-44, claim 1 *	1, 3-6, 9	A 61 L 27/00 // A 61 F 2/06
Y		2, 7, 8, 10-12	
D, Y	FR-A-2 135 433 (D. Vivien) * Page 5, lines 4-10, examples 4-9, claims 1-19	2, 10	
Y	GB-A-1 018 288 (SPOFA) * Page 2, lines 60-127; page 3, example; claims 1, 6, 9 *	7, 8, 11, 12	Areas Searched (Int. Cl.[4]) A 61 L 27/00
A	GB-A-994 275 (M. Gerendas)		
A	DE-A-2 024 341 (INSTITUT PENTRU CONTROLUL DE STAT AL MEDICAMENTULUI SI CERCETARI FARMACEUTICE)		

Reseach location: LE HAYF Date: 3/19/85 Examiner: PELTRE CHR.

CATEGORIES OF CITED DOCUMENTS:

X: Particularly pertinent by itself
Y: Particularly pertinent in combination with another document of the same category
D: Cited in the application
A: Technological background